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Cytokines and pulmonary fibrosis.

Zhang K, Phan SH.

Department of Pathology, University of Michigan, Ann Arbor, USA.

In the past several years, significant progress in many aspects of pulmonary fibrosis research has been made. Among them, the finding that a variety of cytokines play important roles in the complex process appears most intriguing. These cytokines include at least transforming growth factor-beta (TGF-beta), tumor necrosis factor-alpha (TNF-alpha), platelet-derived growth factor, fibroblast growth factors, (TGF-alpha), interleukin-1, monocyte chemoattractant protein-1 and macrophage inflammatory protein-1 alpha. These cytokines have been demonstrated to be produced at the sites of active fibrosis where they appear to be expressed by activated inflammatory cells, such as macrophages and eosinophils. More interestingly, other noninflammatory lung cells including mesenchymal cells, such as myofibroblasts, and epithelial cells, have been found to be significant sources as well, albeit in most instances at somewhat different time points than those by inflammatory cells. Study of the individual cytokines in vitro has revealed a variety of potential roles for these cytokines in the regulation of the fibrotic process in vivo, including chemoattractant, mitogenic activities for fibroblasts, stimulation of extracellular matrix and alpha-smooth muscle actin gene expression, alteration of the contractile phenotype of fibroblasts and regulation of diverse functions of lung inflammatory and epithelial cells which can further impact on the fibrotic process by autocrine and paracrine mechanisms. Of these cytokines, it appears that TGF-beta is probably the most important cytokine in terms of the direct stimulation of lung matrix expression which typifies fibrosis. Recently however, there is accumulating evidence to indicate that the situation is much more complex than any one single cytokine being solely responsible for the fibrotic response. The concept of complex lung cytokine networks, orchestrated by a few key cytokines, such as TNF-alpha, being responsible for this response has received strong support from recent studies. This means that it is the balance of positive (profibrogenic) and negative (antifibrogenic) forces generated from interaction among the various cytokines constituting these networks, which may finally determine the outcome of lung injury and inflammation. The importance of these cytokines also suggests new potential targets for designing new therapies for progressive pulmonary fibrosis, and perhaps their utility in prognostication as well.

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